Amendments to the Specification:

Please replace the paragraph on page 7, lines 16-21 with the following amended paragraph:

Figure 8 shows various splicing patterns of hT1 transcript in different tumor samples. Nested amplification (14 cycles) is performed using HT2026F (SEQ ID No: 115) and HT2482R (SEQ ID No: 119) primers on primary RT-PCR products generated with HT1875F (SEQ ID No: 112) and HT2781R (SEQ ID No: 121) primers. a: Lung carcinoma; b: Lymphoma; c: Lung carcinoma; d: Medulloblastoma; e: Lymphoma; f: Lymphoma; g: T47D; h: Pheochromocytoma; i: Lymphoma; j: Glioma; k: Lymphoma; l: No template control.

Please replace the paragraph on page 7, lines 22-25 with the following amended paragraph:

Figure 9 shows the results of amplification on cDNA synthesized from LIM 1215 cDNA. As shown, reverse transcriptase motif A is deleted from splicing variants containing sequence α. Primer combinations are: a, HTM2028F (SEQ ID No: 116) + HT2356R (SEQ ID No: 118); b, HT2026F (SEQ ID No: 115) + HT2482R (SEQ ID No: 119); c, HTM2028F (SEQ ID No: 116) + HT2482R (SEQ ID No: 119); d. HT2026F (SEQ ID No: 115) + HT2482R (SEQ ID No: 119).

Please replace the paragraph on page 20, lines 19-24 with the following paragraph:

Exon α, located from bases 2131-2166 is frequently observed spliced out of telomerase mRNA. A protein translated from such an RNA is deleted for 12 amino acids, removing nearly all of RTase motif A. This motif appears to be critical for RT function; a single amino acid mutation within this domain in the yeast EST2 protein results in a protein that functions as a dominant negative and results in cellular senescence and telomere shortening.

Please replace the paragraph bridging pages 20-21 with the following amended paragraph:

Another of the variant sequences, the β-exon deletion at base 2286-2468, encodes a truncated protein, due to a reading frameshift at base 2287, which is joined to base 2469, and subsequently a termination codon at base 2605. This variant protein has RTase domains 1, 2, A, B, and part of C, but lacks another motif; in addition to the RTase domain motifs, another sequence motif (AVRIRGKS) (SEQ ID No: 90) identified in the β insert of hT1 matches a P-loop motif consensus AXXXXGK(S) (SEQ ID No: 91) (Saraste et al., *Trends Biochem. Sci. 15*, 430-434, 1990). This motif is found in a large number of protein families including a number of kinases, bacterial dnaA, recA, recF, mutS and ATP-binding helicases (Devereaux et al., *Nucleic Acids Res., 12*, 387-395, 1984). The P-loop is thus present only in a subpopulation of the h-TEL mRNAs in most RNA samples analyzed and completely absent from several tumor samples (Figure 8).

Please replace the paragraph on page 21, lines 16-26 with the following amended paragraph:

In addition to variants that lack the reference C-terminal domain, a variant with exon 3 at base 2157 expresses an alternative C-terminal domain. Furthermore, the coding region donated by exon 3 has a potential SH3 binding site, SGQPEMEPPRRPSGCVG (SEQ ID No: 92), which matches the consensus c-Abl SH3 binding peptide (PXXXXPXXP) (SEQ ID No: 93) found in proteins such as ataxia telangiectasia mutated (ATM). A second example of this motif is found within the N-terminal end of the hT1 protein in the peptide HAGPPSTSRPPRPWDTP (SEQ ID No: 94). Other alternative C-terminal domains are found in telomerase cDNAs; the EST12462 (GenBank Accession No. AA299878) has about 50 bases of identical sequence up to base 2157 and then diverges from the reference telomerase sequence as well as exon 3. This new sequence has an internal stop codon in 50 bases that would result in a truncated C-terminus.

Please replace the paragraph on page 47, lines 14-25 with the following amended paragraph:

To obtain longer clones of hT1, a number of cDNA libraries prepared from tumor cells are screened by amplification using primers from within the EST sequence. Primers HT1553F (SEQ ID No: 108) and HT1920R (SEQ ID No: 114), based on the EST

sequence, are used to amplify an approximately 350 bp fragment in a variety of cDNA libraries. The amplification reaction is performed under "hot start" conditions. Amplification cycles are 4 min at 95°C; 1 min at 80°C; 30 cycles of 30 sec at 94°C, 30 sec at 55°C, 1 min at 72°C°; and 5 min at 72°C. An amplified product of the expected size (~350 bp) is detected in only 3 of the 12 libraries screened. No fragment is detectable in a testis cDNA library, somatic cell libraries, and a variety of cancer cell cDNA libraries. However, an abundant 350 bp fragment is detected in a cDNA library from LIM 1215 cells, a colon cancer cell line. In this library, and in several others, an additional fragment of around 170 bp was amplified.

Please replace the paragraph bridging pages 47-48 with the following amended paragraph:

Two approaches are followed to obtain longer clones from the LIM1215 library: screening plaques with a ^{32}P-labeled EST probe and amplification on library DNA. A single positive plaque, designated 53.2, with a 1.9 kb insert is obtained by hybridization of the library with the EST probe. DNA sequence analysis of this clone demonstrates that it extends both 5' and 3' of the EST sequence, but did not contain a single open reading frame (ORF). A fragment obtained from amplification analysis of the library is similar in sequence to the 53.2 fragment but also contains two additional sequences of 36bp and >300bp. Both insertions demonstrate characteristics of splice acceptor and donor sequences at their boundaries relative to the 53.2 sequence and may represent unspliced exons. Amplification using primers T7 and HT1553F (SEQ ID No: 108), yields an approximately 1.6 kb fragment; and using primers T3 and HT1893R (SEQ ID No: 113), yields an approximately 0.7 kb fragment. Each of these fragments support amplification of a 320 bp fragment using primers HTEL1553F (SEQ ID No: 108) and HT1893R (SEQ ID No: 113).

Please replace the paragraph on page 48, lines 9-22 with the following amended paragraph:

Longer clones may also be obtained by amplification of mRNA samples. Reverse transcriptase PCR (RT-PCR) on LIM1215 mRNA identifies a number of additional PCR products, including one with a 182 bp insertion relative to 53.2 that results in a single open reading frame (ORF). cDNA is synthesized from RNAs isolated from normal and

tumor tissues. RT-PCR followed by nested amplification is performed using the Titan RT-PCR system (Boehringer-Mannheim). Amplification conditions are as follows: 95°C for 2 min, two cycles of 94°C for 30 sec, 65°C for 30 sec and 68°C for 3 min, 2 cycles of 94°C for 30 sec, 63°C for 30 sec, 68°C for 3 min, 34 cycles of 94°C for 30 sec, 60°C for 30 sec and 68°C for 3 min. RT-PCR products are diluted 100 fold, and 1 µl is used for nested amplification using *Taq* polymerase with buffer Q (Qiagen). Amplification conditions are as above, except that the final step is 14 cycles. For normal tissues and tumors, amplification products are resolved by electrophoresis in 1.5% agarose gel, transferred to Zetaprobe membrane and probed with radiolabeled oligonucleotide HT1691F (SEQ ID No: 111).

Please replace the paragraph bridging pages 48-49 with the following amended paragraph:

The DNA sequence is also extended 5' and 3' using a combination of cRACE and 3' RACE, respectively, on LIM1215 mRNA to give a fragment of 3871 bp designated hT1 (Figure 1). Two rounds of cRACE are carried out to extend the sequence of hT1 and map the transcription initiation site. 500 ng LIM1215 polyA+ RNA is used as the template. First strand cDNA synthesis is primed using the HT1576R (SEQ ID No: 109) primer. The first round of amplification on the ligation product (using the XL-PCR system) employs the HT1157R (SEQ ID No: 107) and HT1262F (SEQ ID No: 105) primers. Amplification products are purified using Qiagen columns, and further amplified using primers HT1114R (SEQ ID No: 106) and HT1553F (SEQ ID No: 108). A resulting 1.4 kb band is subjected to DNA sequence analysis, and a new set of primers are designed based on this sequence. For the second round of cRACE, the first strand cDNA is primed with the HT220R (SEQ ID No: 104) primer. The first round of amplification utilizes the HT0142R (SEQ ID No: 102) and HT0141F (SEQ ID No: 101) primers. Products are purified as above and amplified using HT0093 (SEQ ID No: 100) and HT0163F (SEQ ID No: 103) primers. A product of 100 bp is observed and subjected to sequence analysis in two independent experiments to define the 5' end of the hT1 transcript. The 5' end of the transcript is also obtained by amplification using primer HtelFulcodT 5'-AGGAGATCTCGCGATGCCGCGCGCTC-3' (SEQ ID No: 96) and HtelFulcodB 5'-TCCACGCGTCCTGCCCGGGTG-3' (SEQ ID No: 97) on LIM1215 RNA.

E9 The resulting amplified product was digested with Mlu I and Bgl II and ligated to the remaining telomerase cDNA sequence.

Please replace the paragraph on page 49, lines 13-16 with the following amended paragraph:

E10 The 3'-most sequences of the transcript are obtained by two rounds of amplification (XL-PCR system) using EBHT18 (SEQ ID No: 125) in both rounds as the reverse primer, and HT2761F (SEQ ID No: 120) and HT3114F (SEQ ID No: 122) as the forward primers in the first and second rounds, respectively.

Please replace Table 2 bridging pages 49-50 with the following amended Table 2:

E11

Name	Oligo Sequence	Seq Id No:
HT0028F	5' - GCTGGTGCAGCGCGGGGACC	98
HT 5'Met	5' - CACAAGCTTGAATTCACATCTCACCATGAAGGAGCTGGTGGCCC	99
HT0093R	5' - GGCACGCACACCAGGCACTG	100
HT0141F	5' - CCTGCCTGAAGGAGCTGGTG	101
HT0142R	5' - GGACACCTGGCGGAAGGAG	102
HT0163F	5' - CCGAGTGCTGCAGAGGCTGT	103
HT0220R	5' - GAAGCCGAAGGCCAGCACGTTCTT	104
HT1262F	5' - GTGCAGCTGCTCCGCCAGCACA	105
HT1114R	5' - GTTCCCAAGCAGCTCCAGAAACAG	106
HT1157R	5' - GGCAGTGCGTCTTGAGGAGCA	107
HT1553F	5' - CACTGGCTGATGAGTGTGTAC	108
HT1576R	5' - GACGTACACACTCATCAGCCAG	109
HT1590F	5' - GGTCTTTCTTTTATGTCACGGAG	110
HT1691F	5' - CACTTGAAGAGGGTGCAGCT	111
HT1875F	5' - GTCTCACCTCGAGGGTGAAG	112
HT1893R	5' - TTCACCCTCGAGGTGAGACGCT	113
HT1920R	5' - TCGTAGTTGAGCACGCTGAAC	114
HT2026F	5' - GCCTGAGCTGTACTTTGTCAA	115
HTM2028F	5' - CTGAGCTGTACTTTGTCAAGGACA	116
HT2230F	5' - GTACATGCGACAGTTCGTGGCTCA	117
HT2356R	5' - CATGAAGCGTAGGAAGACGTCGAAGA	118
HT2482R	5' - CGCAAACAGCTTGTTCTCCATGTC	119
HT2761F	5' - CTATGCCCGGACCTCCATCAGA	120
HT2781R	5' - CTGATGGAGGTCCGGGCATAG	121
HT3114F	5' - CCTCCGAGGCCGTGCAGT	122
HT3292B	5' - CACCTCAAGCTTTCTAGATCAGTCCAGGATGGTCTTGAAGTCA	123
HT3689R	5' - GGAAGGCAAAGGAGGGCAGGGCGA	124
EBHT18	5' - CACGAATTCGGATCCAAGCTTTTTTTTTTTTTTTT	125
HT-RNA-F	5' - GGGTTGCGGAGGGTGGGC	126
HT-RNA451R	5' - GCAGTGGTGAGCCGAGTCCTG	127

HT-RNA598F	5' - CGACTTTGGAGGTGCCTTCA	128
HTel 5'T	5' - GCTGGTGCAGCGCGGGGACC	129
HTel979T	5' - GAGGTGCAGAGCGACTACTCCA	130
HTell335T	5' - GTCTCACCTCGAGGGTGAAG	131
HTel71T	5' - GGCTGCTCCTGCGTTTGGTGGA	132
HTel21B(Top)	5' - GCCAGAGATGGAGCCACCC	133
HTel21TBot)	5' - GGGTGGCTCCATCTCTGGC	134
HTel-7B	5' - CCGCACGCTCATCTTCCACGT	135
HTel+256B	5' - GCTTGGGGATGAAGCGGTC	136
HtelIntronT	5' - CGCCTGAGCTGTACTTTGTCA	137
Htel 3'CODB	5' - CACCTCAAGCTTTCTAGATCAGCTAGCGGCCCAGCCCAACTCCC	138
Htel 1210B	5' - GCAGCACACATGCGTGAAACCTGT	139
Htel 1274B	5' - GTGTCAGAGATGACGCGCAGGAA	140
Htel 1624b	5' - ACCCACACTTGCCTGTCCTGAGT	141
hTR TAC	5' - ACTGGATCCTTGACAATTAATGCATCGGCTCGTATAATGTGTGGAGGGI GGTGGGC	142
hTR 5'T7	5' - CTGTAATACGACTCACTATAGGGTTGCGGAGGGTGGGC	143
hTR 3'PstI	5' - CACCTGCAGACATGCGTTTCGTCCTCACGGACTCATCAGGCCAGCTGGC GTGTGAGCCGAGTCCTG	144
BT-177	5' - GGATCCGCCGCAGAGCACCGTCTG	145
BT-178	5' - CGAAGCTTTCAGTGGGCCGGCATCTGAAC	146
BT-179	5' - CGAAGCTTTCACAGGCCCAGCCCAACTCC	147
BT-182	5' - GCGGATCCAGAGCCACGTCCTACGTC	148
BT-183	5' - GCGGATCCGTTCAGATGCCGGCCCAC	149

Please replace the paragraph bridging pages 54-55 with the following amended paragraph:

Samples of mRNA are prepared from several different tumors using conventional protocols. The tumors are: (1) SLL lung carcinoma, (2) Lymphoma C, (3) Lung carcinoma, (4) Medullablastoma A, (5) Lymphoma B, (6) Lymphoma E, (7) Tumor sample 47D, (8) Pheochromocystoma, (9) Lymphoma F, (10) Glioma, and (11) Lymphoma G. The mRNAs from these samples are first reverse transcribed to cDNAs and then amplified using primers HT1875F (SEQ ID No: 112) and HT2781R (SEQ ID No: 121), followed by amplification with nested primers HT2026F (SEQ ID No: 115) and HT2482R (SEQ ID No: 119). Four different amplified products are observed in Figure 8: 220 bp (band 1), 250 bp (band 2), 400 bp (band 3) and 430 bp (band 4). Strikingly, there is considerable variation among the tumor samples tested both in the total number of amplified products and in the quantitative distribution among the products.

Please replace the paragraph bridging pages 55-56 with the following amended paragraph:

To test the hypothesis that such a transcript exists, a primer, HTM2028F, is designed such that amplification ensues only when the 36 bp fragment was missing. Amplification using HTM2028F (SEQ ID No: 116) and HT2026F (SEQ ID No: 115) primers in combination with HT2356R (SEQ ID No: 118) demonstrate that transcripts containing the 182 bp fragment but missing the 36 bp fragment are present in LIM1215 RNA (Figure 9, lanes a and b). The same top strand primers (HTM2028F (SEQ ID No: 116) and HT2026F (SEQ ID No: 115)) in combination with HT2482R (SEQ ID No: 119) primer amplify a number of products from LIM1215 RNA (Figure 9, lanes c and d), most of which represent bands 1- 4 as determined by direct sequence analysis of PCR products. An amplified fragment of 650 bp using HTM2028F (SEQ ID No: 116) and HT2482R (SEQ ID No: 119) primers represents another, not yet fully characterized, alternatively spliced telomerase variant in the RT-MotifA/RT Motif B region. For clarity of presentation, the protein sequence giving the best match with *Euplotes* and *S. cerevisiae* proteins is presented in Figure 1 as the reference sequence.

Please replace the paragraph on page 56, lines 4-24 with the following amended paragraph:

Specifically, there are at least seven inserts or exons that can be present (or absent) from telomerase RNA. (1) The 5'-most sequence (Y) is located between bases 222 and 223. (2) the insert (X) is located between bases 1766 and 1767. A partial sequence is determined and is presented in Figure 10. Termination codons are present in all three reading frames. Thus, a truncated protein without any of the RTase motifs would be produced. (2) A sequence, indicated as "1" in Figure 7, is located between bases 1950 and 1951. This exonic sequence is 38 bp (Figure 10) and appears to be present in ALT and most tumor lines. The presence of this sequence adds 13 amino acids and shifts the reading frame, such that a termination codon (TGA) is in frame at nucleotide 1973. (3) A sequence, indicated as "α" in Figure 7, is located between bases 2130 and 2167. This sequence is 36 bp (Figure 10) and its absence removes RTase motif "A" but does not alter the reading frame. (4) A sequence, indicated as "β" in Figure 7 is present between bases 2286 and 2469. The insert is 182 bases

(Figure 10) and its absence causes a reading frame-shift and a termination codon in RTase motif 5 at nucleotide 2604. (5) The sequence "2" in Figure 7 is present between bases 2823 and 2824. Its length is undetermined; its partial sequence is presented in Figure 10. The presence of this insert causes a truncated telomerase protein, as the first codon of the insert is a termination codon. (6) The sequence "3" is a 159 bp insert (Figure 10) between bases 3157 and 3158. Its presence leads to a telomerase protein with an altered COOH-terminus. The insert contains a stop codon. Moreover, sequence "3" has a putative binding site for the SH3 domain of c-*abl* (PXXXXPXXP (SEQ ID No: 93); PEMEPPRRP (SEQ ID No: 150)).

Please replace the paragraph on page 57, lines 7-19 with the following amended paragraph:

For the amplification, first strand cDNA is synthesized and used in an amplification reaction (Titan system, Boehringer, IN) with a mixture of DNA polymerases, such that a proofreading thermostable enzyme (*e.g.*, *rTth*)is used with *Taq* DNA polymerase. As much of the mRNA in LIM 1215 lacks sequence B (Figure 9), the amplification primers are designed such that one primer of each pair is within sequence B, on either side of the *Sac* I site at nucleotide 2271 (Figure 1). The 5' portion is first amplified from cDNA using HT2356R (SEQ ID No: 118) and HT0028F (SEQ ID No: 98) primers (cycle conditions: 70° C, 2 min; then added primer sequences equilibrated to 50°C; 50°C, 30 min; 95°C, 2 min; 2 cycles of 94°C, 30 sec; 65°C, 30 sec; 3 cycles of 94°C, 30 sec; 63°C, 30 sec; 68°C 3 min; 32 cycles of 94°C, 30 sec; 60°C, 30 sec; 68°C, 3 min). The extreme 5' portion of the telomerase gene is then ligated in *Eco* RI/ *Sac* I digested pTTQ18 (Amersham International plc, Buckinghamshire, England) and pBluescriptII KS+, and the sequence verified.

Please replace the paragraph on page 57, lines 20-24 with the following amended paragraph:

To obtain the 3' end, LIM 1215 cDNA is amplified using HT2230F (SEQ ID No: 117) and a HT3292B (SEQ ID No: 123) primer that is complementary to the sequence encoding the very C-terminus of telomerase. The amplification products are digested with *Hind* III and *Sac* I and inserted into pTTQ18 and pBluescript II KS+. The 5' and 3' ends are

also cloned joined at the native *Sac* I site in pTTQ18 both as a Hexa-His fusion and a non-fusion protein.

Please replace the paragraph on page 58, lines 16-20 with the following amended paragraph:

The human telomerase RNA component is first isolated by amplification from genomic DNA. The amplification primers are telRNA T (SEQ ID No: 126) and telRNA 598B (SEQ ID No: 128) (Figure 5). Amplification conditions are 95°C, 3 min; addition of polymerase; 80°C 2 min; 35 cycles of 94°C, 30 sec; 68°C, 2 min.

Please replace the paragraph on page 58, lines 21-24 with the following amended paragraph:

The amplified product is inserted into pBluescript after another amplification using hTR TAC (SEQ ID No: 142) (has a tac promoter sequence) and hTR 3'Pst (SEQ ID No: 144) (has a cis-acting ribozyme sequence) primers. The pBluescript insert is then isolated and ligated to pACYC177.

Please replace the table on page 59 with the following amended paragraph:

Fragment ID	Primers	Amino acids
I	BT-177 / BT-178 (SEQ ID No: 145)/ (SEQ ID No: 146)	AAEH...→ ...VQMPAH (SEQ ID No: 151)...→ ... (SEQ ID No: 152)
II	BT-177 / BT-179 (SEQ ID No: 145)/ (SEQ ID No: 147)	AAEH... → ...VGLGL (SEQ ID No: 151)...→ ... (SEQ ID No: 153)
III	BT-182 / BT-179 (SEQ ID No: 148)/ (SEQ ID No: 147)	RATS... → ...VGLGL (SEQ ID No: 154)...→ ... (SEQ ID No: 153)
IV	BT-183 / BT-179 (SEQ ID No: 149)/ (SEQ ID No: 147)	VQMPAH...→ ...VGLGL (SEQ ID No: 152)...→ ... (SEQ ID No: 153)

Please replace the paragraph bridging pages 59-60 with the following amended paragraph:

Fragment I encodes the "fingers and palm" domain that corresponds to MoMuLV. The C-terminal "thumb" and "connection" (see, Kohlstaedt et al., *Science 256*: 1783, 1992) are deleted. Fragment II encodes the telomerase reverse transcriptase domain, as

well as the C-terminal "connection" domain. The N-terminus is chosen by size comparison with the MoMuLV RTase structure. Fragment III encodes the C-terminus of the protein. The RATS sequence is located within the RTase domain (palm region) of the protein. Fragment IV encodes the C-terminal region containing the "thumb" and "connection" domains and may function as a regulatory element. The connection domain in HIV-1 is able to block the catalytic cleft of HIV RTase in the absence of the RNase domain (Kohlstaedt et al, *supra*). In an analogous fashion, the C-terminal region may be useful as a regulatory (inhibitory) fragment. Moreover, sequence C has a putative binding site for the SH3 domain of c-*abl* (PXXXXPXXP (SEQ ID No: 93); PEMEPPRRP (SEQ ID No: 150), see variant 2 sequence of Figure 8). c-*abl* protein interacts directly with the ATM (ataxia telangiectasia) protein (Shafman et al., *Nature 389:* 520, 1997), a protein apparently involved in cell-cycle control, meiotic recombination, telomere length monitoring and DNA damage response. Binding of c-*abl* protein may be assessed in standard protein-protein interaction methods. As such, an interaction of telomerase and c-*abl* or other SH3-domain containing proteins (*e.g.*, erb2) and regulation by movement of the telomerase C-terminus in and out of the catalytic cleft may be controllable using the constructs and products described herein. In one instance, regulation may be mediated by phosphorylation/dephosphorylation reactions.